Dofetilide
Criteria for Use
May 2016

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

The Product Information should be consulted for detailed prescribing and safety information.

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive dofetilide*

- ☐ Congenital or acquired long QT syndromes
- ☐ Baseline QT interval or QTc > 440 msec (500 msec in patients with ventricular conduction abnormalities e.g., bundle branch blocks or intraventricular conduction delays [IVCD])
- ☐ Severe renal impairment (calculated creatinine clearance [CrCl] per Cockcroft-Gault using actual body weight < 20 ml/min)
- ☐ Patients receiving treatment with verapamil, cimetidine, trimethoprim (alone or in combination with sulfamethoxazole), ketoconazole, prochlorperazine, dolutegravir, megestrol, hydrochlorothiazide (alone or in combination with triamterene) (refer to Monitoring for additional potential Drug Interactions)
- ☐ Concomitant use with drugs that prolong the QT interval, or Class I or other Class III antiarrhythmic drug therapy (refer to Monitoring)
- ☐ Known hypersensitivity to dofetilide

Inclusion Criteria *The answers to the following must be fulfilled in order to meet criteria for dofetilide*

☐ Initial prescription[#] restricted to VA Cardiology or local designee (monitoring must be documented by a VA provider) (refer to Issues for Consideration)

☐ Atrial fibrillation/atrial flutter (highly symptomatic*) in patients who require cardioversion to normal sinus rhythm (Refer to table below)

Recommendations for Pharmacologic Cardioversion of Atrial Fibrillation/Atrial Flutter[a]	***Recommendation Class (Level of Evidence)***
• **Flecainide**, **propafenone**, dofetilide, IV ibutilide are useful for cardioversion of atrial fibrillation or atrial flutter (if there are no contraindications)	I (A)
• **Amiodarone** is reasonable for pharmacologic cardioversion of atrial fibrillation	IIa (A)
• **Propafenone** or **flecainide** ("pill-in-the pocket") is reasonable to terminate atrial fibrillation out of the hospital after observed to be safe in a monitored setting	IIa (B)
• Dofetilide should not be initiated out of the hospital	III: Harm (B)

[a]Adapted from 2014 AHA/ACC/HRS Guideline for the management of patients with Atrial Fibrillation (JACC 2014)

[#] *If dofetilide is being initiated, re-initiated, or the dose increased, use is restricted to inpatient admission for appropriate monitoring and dose adjustments (refer to Boxed Warning, Dosage and Administration, Monitoring, Dosing Algorithm)*

**Dofetilide can cause life threatening ventricular arrhythmias, it should be reserved for patients in whom atrial fibrillation/atrial flutter is highly symptomatic*

OR

☐ Maintenance of normal sinus rhythm in patients with highly symptomatic* atrial fibrillation/atrial flutter who have been converted to normal sinus rhythm (Refer to table below)

Considerations for Pharmacologic Rhythm Control in Patients with Paroxysmal or Persistent Atrial Fibrillation[a]

<u>No Structural Heart Disease</u>	<u>Coronary Artery Disease</u>	<u>Heart Failure</u>
Amiodarone[b]	**Amiodarone[b]**	**Amiodarone[b]**
Dofetilide[c,d]	**Dofetilide[c,d]**	**Dofetilide[c,d]**
Flecainide[c,e]	**Sotalol[c,d]**	
Propafenone[c,e]	*Dronedarone[f]*	
Sotalol[c,d]		
Dronedarone[f]		

VA National Formulary agents (bolded) listed in alphabetical order (not by treatment preference), non-formulary agent (italicized) listed last

[a] Adapted, in part, from 2014 AHA/ACC/HRS Guideline for the management of patients with Atrial Fibrillation (JACC 2014)

[b] Consider risk vs. benefit; individualize therapy

[c] Not recommended in patients with severe left ventricular hypertrophy (wall thickness > 1.5 cm)

[d] Use with caution in patients at risk for torsades de pointes

[e] Should be combined with atrioventricular nodal blocking agents

[f] Dronedarone is non-formulary in VA; refer to National VA PBM-MAP-VPE Dronedarone Criteria for Use

**Dofetilide can cause life threatening ventricular arrhythmias, it should be reserved for patients in whom atrial fibrillation/atrial flutter is highly symptomatic*

Dosage and Administration (refer to Dofetilide Dosing Algorithm and/or Dofetilide Product Information)

- Dofetilide must be initiated where continuous electrocardiogram (ECG) monitoring can be provided and in the presence of personnel trained in the management of serious ventricular arrhythmias. The above recommendations also apply to patients who may require re-initiation of dofetilide. Patients should be monitored as above for a minimum of 3 days while on dofetilide or for 12 hours after conversion to normal sinus rhythm, whichever is longer.
- The dose of dofetilide is determined based on calculated CrCl and QTc (use QT interval if heart rate < 60 beats per minute; no data in patients with heart rate < 50 beats per minute). Refer to Dofetilide Dosing Algorithm and/or Product Information for dosing recommendations.
- In addition to CrCl and QTc, the provider may consider additional patient specific factors that may increase the risk for torsades de pointes and choose a lower dose of dofetilide. As the risk for torsades de pointes increases with increased doses of dofetilide, patients determined to be a candidate for an increase in dose require re-hospitalization for at least 3 days in order for appropriate care and monitoring to take place. The maximum dose of dofetilide is 500 mcg twice daily.
- The recommended dosing interval for dofetilide is twice daily (i.e., every 12 hours), with the patient instructed to take the medication at the same time each day. If dofetilide is administered once daily (refer to Dosing Algorithm or Product Information), the dose should be administered at the same time each day.

Monitoring

- **QTc:** It is generally recommended to evaluate ECG every 3 months (or as medically indicated) during therapy with dofetilide. Long-term data on the optimal frequency of monitoring ECG is unknown. If the QTc (use QT interval if heart rate < 60 beats per minute) increases to > 500 msec (550 msec if ventricular conduction abnormalities e.g., paced rhythm [refer to Issues for Consideration], bundle branch blocks or IVCD), dofetilide should be discontinued and the patient monitored carefully until the QTc returns to baseline.
- **Renal function:** Evaluate serum creatinine (and calculate CrCl) every 3 months for the first year then every 3 to 6 months thereafter (or as medically indicated) during therapy with dofetilide. If renal function declines, the dose of dofetilide should be adjusted according to the initial dosing recommendations based on CrCl (refer to Dofetilide Dosing Algorithm and/or Product Information for dosing recommendations).
- **Electrolytes:** Due to the increased risk for proarrhythmias, serum potassium and magnesium should be maintained within the normal range before and during treatment with dofetilide. General recommendations are to tightly control potassium (e.g., if < 4.0 mEq/L; per the Product Information, potassium generally maintained above 3.6 to 4.0 mEq/L in clinical trials) and magnesium (e.g., if < 2 mg/dl) levels.
- **Anticoagulation:** Patients with atrial fibrillation should be anticoagulated according to usual medical practice prior to cardioversion; with anticoagulation continued as indicated for atrial fibrillation as per usual medical practice.
- **Cardioversion:** If dofetilide is being initiated for pharmacologic cardioversion of atrial fibrillation/atrial flutter and the patient does not convert to normal sinus rhythm within 24 hours, electrical cardioversion should be considered. Patients continued on dofetilide after successful electrical cardioversion should be monitored by ECG for 12 hours after conversion, or for a minimum of 3 days after initiation of dofetilide, whichever is greater.
- **Switching to dofetilide from other antiarrhythmic drug therapy:** Before initiating therapy with dofetilide, patients on Class I or Class III antiarrhythmic drug therapy should be withdrawn under careful monitoring for a minimum of 3 plasma half-lives. If the patient has been treated with amiodarone, dofetilide should not be initiated until amiodarone levels are < 0.3 mcg/ml, or until amiodarone has been withdrawn for at least 3 months.
- **Adherence:** The patient should be informed of the importance of adherence and not to miss a dose of dofetilide. If the patient misses a dose, they should be instructed not to double the next dose and to take their next dose at the usual time. Upon discharge from the hospital, the patient should be provided with an adequate supply of dofetilide until they are able to fill their prescription.
- **Drug interactions:**
  - Due to the linear relationship with dofetilide concentrations and QTc, medications that may interfere with the metabolism (e.g., dofetilide is metabolized to a small degree by CYP3A4 isoenzyme) or renal elimination (e.g., dofetilide is eliminated by cationic renal secretion) of dofetilide may increase the risk for torsades de pointes. Medications that cause hypokalemia or hypomagnesemia may also increase the risk for torsades de pointes. Use of dofetilide with other medications that prolong the QT interval (e.g., phenothiazines, cisapride, bepridil, tricyclic antidepressants, certain fluoroquinolones, certain oral macrolides) has not been studied and is not recommended. Also refer to recommendations above on switching patients currently receiving Class I or Class III antiarrhythmic drug therapy.
  - Dofetilide is contraindicated with the following medications: verapamil, cimetidine, trimethoprim (alone or in combination with sulfamethoxazole), ketoconazole, prochlorperazine, dolutegravir, megestrol, hydrochlorothiazide (alone or in combination with triamterene). Hydrochlorothiazide may reduce serum potassium levels as well as increase plasma concentrations of dofetilide; chlorthalidone has not been specifically studied with dofetilide but may also reduce serum potassium levels (some drug interaction resources list thiazide or thiazide-type diuretics as contraindicated or to avoid combination with dofetilide).
  - Other potential drug interactions with dofetilide include: triamterene (alone or in combination with hydrochlorothiazide), metformin, amiloride (also eliminated by renal cationic secretion); macrolide antibiotics, azole antifungal agents, protease inhibitors, serotonin reuptake inhibitors, amiodarone, cannabinoids, diltiazem, grapefruit juice, nefazodone, quinine, zafirlukast (CYP3A4 isoenzyme inhibitors). Caution should be used with the concomitant use of these agents with dofetilide. Patients receiving dofetilide in conjunction with digoxin should be monitored for digoxin toxicity. Concomitant use of dofetilide and digoxin was also associated with a higher risk of torsades de pointes (unknown if due to drug interaction or presence of structural heart disease in patients on digoxin).
  - If the patient requires withdrawal of dofetilide in order to allow for initiation of a potentially interacting medication, there should be a wash-out period of at least 2 days before starting the other medication.

- The patient's medication profile should be reviewed for changes to any medications that may interact with dofetilide; adjust treatment or provide follow-up and monitoring as indicated. It is recommended to perform medication reconciliation and provide patient with most recent active medication list.

Issues for Consideration

- **FDA indications:** Dofetilide is approved for:
  - **Maintenance of normal sinus rhythm (delay in time to recurrence of atrial fibrillation/atrial flutter)** in patients with atrial fibrillation/atrial flutter of > 1 week duration who have been converted to normal sinus rhythm. Because dofetilide can cause life threatening ventricular arrhythmias, it should be reserved for patients in whom atrial fibrillation/atrial flutter is highly symptomatic.
  - **Conversion of atrial fibrillation/flutter** to normal sinus rhythm.
- **Local provider restrictions:** It is recommended that the patient be evaluated by a VA Cardiologist to obtain an initial VA prescription for dofetilide (e.g., if the patient is continuing therapy initiated by an outside provider); if feasible and deemed appropriate. Alternatively, sites may establish a mechanism for patients to be evaluated for an initial VA prescription by a designated provider(s) (e.g., providers previously certified via the dofetilide Risk Evaluation and Mitigation Strategy [REMS] program or other designee). Whether the VA provider is initiating therapy, continuing therapy initiated by an outside provider, or renewing a VA prescription, appropriate follow-up and monitoring must be documented by a VA provider. Note: If dofetilide is being initiated, re-initiated, or the dose increased, use is restricted to Cardiology and inpatient admission for appropriate monitoring and dose adjustments (refer to Boxed Warning, Dosage and Administration, Monitoring, Dosing Algorithm).
- **Risk for torsade de pointes; inpatient initiation, re-initiation, or dose increase :**
  - Although the REMS program for dofetilide has been eliminated as of March 9, 2016, the FDA recommends that "Prescribers should continue to follow the labeled directions for initiation and dose selection of Tikosyn [dofetilide] in order to minimize the risk of induced ventricular arrhythmias". FDA Information for Tikosyn (dofetilide) available at: *http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm489271.htm*

Boxed Warning

To minimize the risk of induced arrhythmia, patients initiated or re-initiated on dofetilide should be placed for a minimum of 3 days in a facility that can provide calculations of creatinine clearance, continuous electrocardiographic monitoring, and cardiac resuscitation. For detailed instructions regarding dose selection, see Dosage and Administration.

  - The overall incidence of torsade de pointes was reported in 0.8% of patients with supraventricular arrhythmias treated with dofetilide. In clinical trials with dofetilide, torsade de pointes was reported in 3.3% of patients with heart failure, and 0.9% in patients with recent myocardial infarction; the majority of which occurred within the first 3 days of therapy, and the risk for which was reported to be decreased after dose adjustments based on recommended monitoring. Although there was an increased risk for torsade de pointes with dofetilide, mortality was not increased in these trials that included the 3 day inpatient initiation of dofetilide. Patients should also receive education on the risk vs. benefit of treatment with dofetilide and to contact their provider if they feel faint, become dizzy, or pass-out.
- **Paced rhythm:** Patients with pacing devices and QTc > 500 msec prior to initiation of dofetilide, or > 550 msec while on treatment with dofetilide should be treated under the direction of a Cardiologist with expertise in electrophysiology.
- **Off-label use:** Dofetilide has also been evaluated (small studies) for: prevention of recurrent paroxysmal supraventricular tachycardia (similar results vs. propafenone), prevention of inducible ventricular tachycardia (VT) in patients non-responsive to previous antiarrhythmic therapies (prevention in 49% of patients), potential reduction in implantable cardioverter-defibrillator (ICD) interventions for VT or ventricular fibrillation (VF) (mixed-results); these or other off-label uses (e.g., limited or retrospective data with dofetilide in management of early recurrence of atrial fibrillation or flutter post-ablation) should be determined on a case by case basis, taking into consideration the risk vs. benefit
- **Pregnancy Category C:** There are no adequate and well-controlled studies in pregnant women. Dofetilide should only be administered to pregnant women where the benefit justifies the potential risk to the fetus. Refer to the dofetilide product information regarding results of animal studies.

Discontinuation Criteria

- QTc > 500 msec (550 msec if ventricular conduction abnormalities e.g., paced rhythm [refer to Issues for Consideration], bundle branch blocks or IVCD) (use QT interval if heart rate < 60 beats per minute)
- CrCl < 20 ml/min
- Patient is not tolerating therapy with dofetilide
- Patient is to begin therapy with an interacting medication that is contraindicated with the use of dofetilide; refer to Drug interaction section under Monitoring
- Atrial fibrillation becomes permanent

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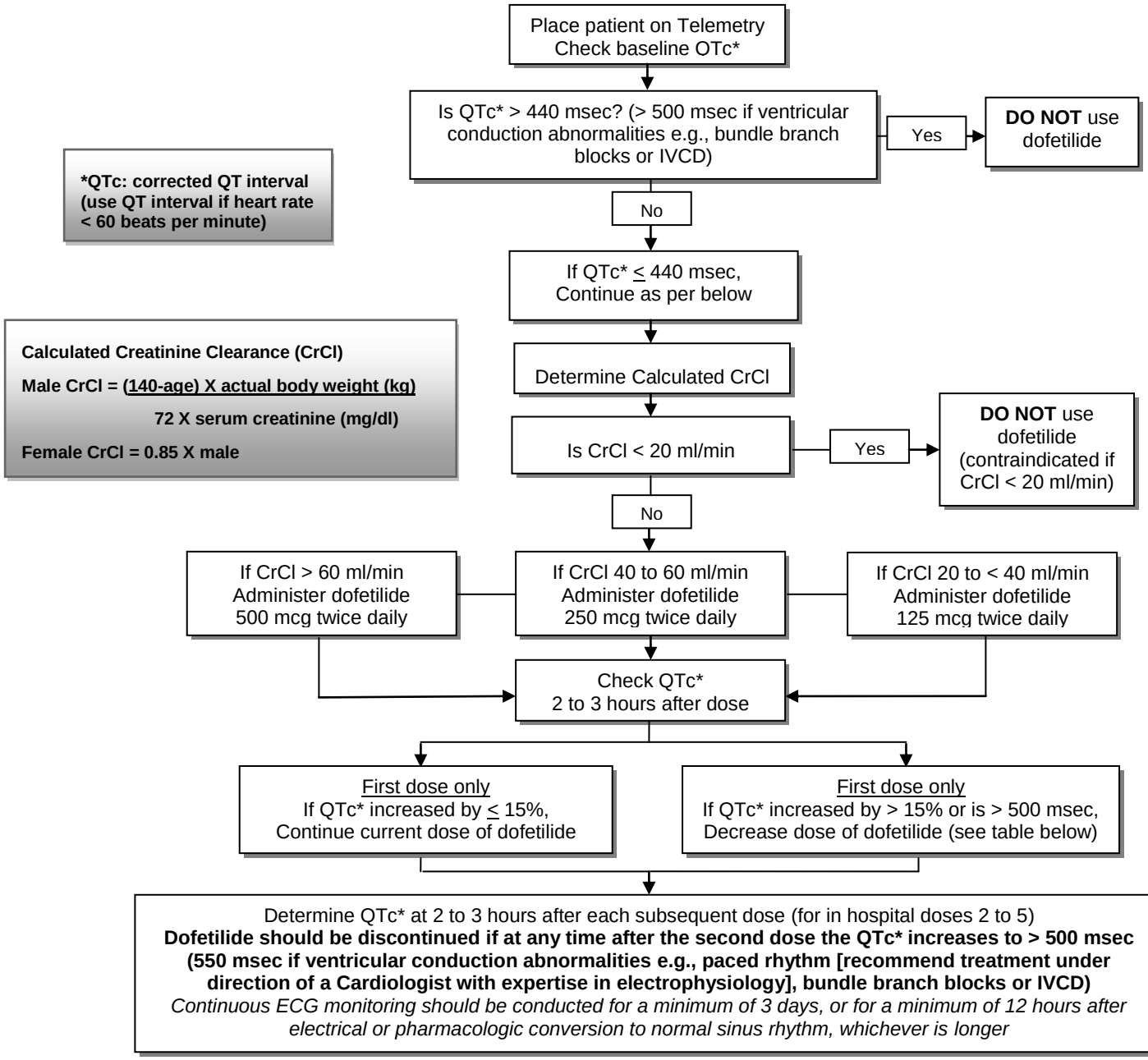
Dofetilide Dosing Algorithm

(Adapted from Dofetilide Product Information)



***QTc: corrected QT interval (use QT interval if heart rate < 60 beats per minute)**

Calculated Creatinine Clearance (CrCl)

Male CrCl = (140-age) X actual body weight (kg)
72 X serum creatinine (mg/dl)

Female CrCl = 0.85 X male

Adjusted Dose if QTc* Prolongation (see above) [Note: only 1 down titration for QTc* suggested]

Starting Dose	*Decreased Dose*
500 mcg twice daily	250 mcg twice daily
250 mcg twice daily	125 mcg twice daily
125 mcg twice daily	125 mcg once daily